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Plasma Cortisol in Men – Relationship With Atherosclerosis of Retinal Arteries

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A B S T R A C T

The production of cortisol increases in acute stress but the effects of chronic stress on plasma cortisol are still controversial. Stress on the other hand plays a role in coronary artery disease (CAD) and carotid atherosclerosis. Since there is no data about plasma cortisol and atherosclerosis of the retinal arteries, the purpose of this study was to explore the relationship between plasma cortisol in 101 adult males with the degree of their retinal vessels atherosclerosis. The results were compared with those in 47 matched apparently healthy men with no retinal vessels changes. The atherosclerotic changes of retinal vessels were determined by direct ophthalmoscopy and graded (1–4) according to Scheie. Morning plasma cortisol levels were determined by radioimmunoassay using commercial kits. The results were compared by using chi-square test. No association between morning plasma cortisol concentrations and retinal vessels atherosclerosis could be found. The results of this study do not support a role for physiological levels of plasma cortisol in the development of atherosclerosis, at least of the retinal arteries, in men.

Introduction

Several studies have indicated that psychosocial factors play a role in coronary artery disease (CAD)[1–4]. This seems to be true for atherosclerosis of the carotid arteries as well[5–7]. However, the exact pathophysiological mechanisms by which psychosocial stress could cause increased atherosclerosis risk in coronary and carotid arteries, have not been established yet. It has been hypothesized that changes in the function of the hypothalamo-pituitary-adrenal (HPA) axis i.e. »exhausted axis« form the pathway of this increased risk since CAD is associ-

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ated with metabolic syndrome and NIDDM[8]. It is well known that the production of cortisol increases in acute stress having and impact on many organ systems. This occurs as a result of psychological stress[9,10], but even more as a result of other stress stimuli such as noise[11], acceleration[12], and different surgical procedures[13–17]. The effect of cortisol on cardiovascular system is primarily due to its inotrope effect and due to increasing and prolonging the effects of adrenaline and glucagon[18].

Hence, studies about the production of cortisol in states of chronic stress produced conflicting results. Some studies have found chronic stress to be associated with increased cortisol concentrations in people suffering from endogenous depression[19] and chronic burnut[20] but the others have found reduced cortisol response among men in countries in transition[21], unemployed[22,23], and people with posttraumatic stress disorder[24].

Although atherosclerotic changes have been described in the retinal arteries half a century ago, there is no data about plasma cortisol and retinal artery atherosclerosis. The purpose of this study was to analyze the relationship between morning plasma cortisol concentration and atherosclerosis of retinal arteries in adult men.

Materials and Methods

Subjects

The study group consisted of 101 males with atherosclerotic changes of retinal arteries and an age, smoking and BMI matched control group of 47 males with normal eye fundus. Neither of the subjects was acutely ill nor was receiving any steroids, lipid lowering agents, antihypertensives or any other drugs known to influence steroid hormones at the time of the study and over the 3 months prior to the study. Exclusion criteria were: diabetes or impaired glucose tolerance, hypertension (BP higher than 140/90 mmHg), clinical adrenocortical hyperfunction or insufficiency, clinical hypo- or hyperthyreosis, clinical liver disease, clinical renal disease, chronic or acute pancreatitis, former or present malignant disease, autoimmune diseases, extreme obesity (BMI >35), a history of drug abuse and/or a history of alcohol consumption greater than 21 units per week, as well as a history of myocardial infarction, angioplasty, stroke, or major surgery during the 6 months preceding the study.

The study complied with the Declaration of Helsinki. All subjects received oral and written information concerning the study prior to giving written informed consent.

Analysis of the retinal arteries

In all the subjects the eye fundus examination was carried out by direct ophthalmoscopy performed after the pupil dilatation by the same ophthalmologist. The atherosclerotic vascular lesions in the retinal arteries were classified according to Scheie[25,26]. Namely, Scheie developed a four-scale classification of atherosclerotic changes of retinal arteries which was used in this study:

Stage 1 – A broadening of the light reflex from the artery can be seen, with minimal or no arteriovenous compression. This is the earliest sign of retinal artery atherosclerosis.

Stage 2 – The changes are similar to those in Stage 1 but more prominent.

Stage 3 – The arteries have a »copper wire« appearance and there is much more arteriovenous compression. These are serious atherosclerotic changes of retinal arteries.

Stage 4 – The arteries have a »silver wire« appearance and the arteriovenous crossing changes are most severe. This is

the most severe form of the atherosclerosis of the retinal arteries.

Measurements of plasma cortisol

Morning fasting venous blood samples were taken from all subjects between 8 and 9 a.m. after an overnight fast and 15 min of rest in the supine position. Samples were centrifuged at –4 °C within 15 minutes of collection and were analyzed the same day.

Plasma cortisol concentration was measured using radioimmunoassay[27] with commercial kits by Diagnostic Products Corporation, USA. Normal values were 138–690 nmol/l.

Statistical analysis

Plasma morning cortisol concentrations for patients with retinal artery atherosclerosis and subjects with no retinal artery changes were compared by using χ^2 test. Statistical significance was assumed for p less than 5% ($p < 0.05$).

Results

Patients with the atherosclerosis of retinal arteries were 49.56 +/– 9.68 years old (range 26 – 69 years) and had a BMI 24.6 +/–2.8. Controls were 47.79 +/–10.30 years old (range 22 – 65 years) and had a BMI 24.0 +/– 2.1.

No significant correlation between retinal vessels atherosclerosis and morning plasma cortisol concentrations could be proved (χ^2=0.4545; df=2; p>0.1). When the analysis of the degree of atherosclerotic changes of the retinal arteries was performed again no significant association with plasma cortisol could be found (Table 1).

TABLE 1
THE STAGE OF THE ATHEROSCLEROTIC CHANGES OF THE RETINAL ARTERIES AND MORNING PLASMA CORTISOL CONCENTRATION

		Cortisol (nmol/l)			
Retinal arteries		< 138	138–690	> 690	Total
Normal	a	2	38	7	47
	b	4.3	80.9	14.9	31.8
	c	40.0	30.6	36.8	0
Stage 1	a	0	26	1	27
	b	0	96.3	3.7	18.2
	c	0	21.0	5.3	0
Stage 2	a	1	28	4	33
	b	3.0	84.8	12.1	22.3
	c	20.0	22.6	21.1	
Stage 3	a	2	26	5	33
	b	6.1	78.8	15.2	22.3
	c	40.0	21.0	26.3	0
Stage 4	a	0	6	2	8
	b	0	75.0	25.0	5.4
	c	0	4.8	10.5	0
Total	a	5	124	19	148
	b	3.4	83.8	12.8	100.0

a = number of subjects; b = % horizontal; c = % vertical; ^{2} = 5.71523, df = 8, p > 0.1

Discussion

Although almost four decades ago it has been noticed that 73% of patients with atherosclerotic retinal changes have atherosclerotic changes of other arteries as well, while 72% of the patients with atherosclerotic lesions in some other arteries have also atherosclerotic changes of the retinal arteries[28–30], correlation between plasma cortisol and retinal artery atherosclerosis have not been previously examined. Despite the limitations of the use of plasma cortisol values for assessing the effects of stress because they reflect only short time spans, all the other methods are not feasible in epidemiological studies. Namely neither invasive methods, nor urine excretion measured over the course of 24 h or measurements of cortisol in saliva[31] are appropriate for such studies. Therefore we have decided to use morning plasma cortisol concentration.

The plasma cortisol levels did not vary for persons with more and less severe atherosclerotic changes of the retinal arteries. The reason for this may be that average cortisol levels do not have impact on atherosclerosis. However, several studies have indicated that the reactivity of HPA axis together with changes in the sympathetic nervous system could effect the development of atherosclerosis[8,32] but according to other studies there is no association between HPA reactivity and chronic stress[22]. Excessive and sustained cortisol secretion or chronic pharmacological doses of glucocorticoids (endogenous or exogenous Cushing syndrome) have been long associated not only with osteoporosis and immunosuppression but also with hypertension, dyslipidemia and syndrome X causing atherosclerosis and CAD[33]. The results of some studies suggest that even normal life stress related hypersecretion of cortisol could effect blood pressure and body mass index[34] and therefore maybe atherogenesis. However, it is questionable whether an altered daily cortisol secretion variance could result with somatic sequel of chronic hypercortisolism. On the other hand, blunting of the circadian rhythm could result in evening exposure to cortisol, which could be detrimental on its own in spite of an adequate correction of time integrated cortisol secretion. For example, a case of an adult man with Carney complex treated in childhood with unilateral adrenalectomy has been reported and although his 24h urinary free cortisol excretion remained normal for many years, he developed severe osteoporosis, possibly as a result of constant exposure of his bones to »normal« levels of plasma cortisol[35]. The similar situation might be with atherosclerosis. Therefore our results showing no correlation between morning plasma cortisol levels and atherosclerosis of the retinal vessels do not negate the role of cortisol in atherogenesis in general but for a more thorough understanding of the impact of cortisol on atherosclerosis, not only of retinal arteries, large prospective studies are needed.

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KORTIZOL U PLAZMI MUŠKARACA: POVEZANOST S ATEROSKLEROZOM MREŽNIČNIH ARTERIJA

S A Ž E T A K

Lučenje kortizola povećava se u akutnom stresu no učinci kroničnog stresa na kortizol još su dvojbeni. S druge pak strane stres igra ulogu u nastanku koronarne bolesti srca i ateroskleroze karotidnih arterija. Budući da nema nikakvih podataka o koncentraciji kortizola u plazmi i aterosklerozi mrežničnih arterija, cilj je ovog istraživanja bio ustanoviti ima li kakve povezanosti između kortizola u plazmi 101 muškarca i postojanja te stupnja uznapredovalosti ateroskleroze arterija mrežnice. Rezultati su uspoređeni s onima u 47 zdravih muškaraca podjednake dobi i ostalih obilježja koji nisu imali nikakvih promjena na arterijama mrežnice. Aterosklerotičke promjene arterija mrežnice procjenjivane su uz pomoć direktne oftalmoskopije i stupnjevane su od 1 do 4 prema Scheieu. Koncentracija kortizola u krvi određivana je ujutro uz pomoć radioimunoeseja uz uporabu komercijalnih testova. Rezultati su uspoređeni hi-kvadrat testom. Nije dokazana nikakva povezanost između koncentracije kortizola u plazmi ujutro i ateroskleroze mrežničnih arterija. Rezultati ovog istraživanja ne govore u prilog tome da kortizol u plazmi sudjeluje u nastanku ateroskleroze, barem ne arterija mrežnice, u muškaraca.